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Is continuous infusion of imipenem always the best choice?

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ABSTRACT

Monte Carlo simulations allow prediction and comparison of concentration–time profiles arising from different dosing regimens in a defined population, provided a population pharmacokinetic model has been established. The aims of this study were to evaluate the population pharmacokinetics of imipenem in critically ill patients with hospital-acquired pneumonia (HAP) and to assess the probability of target attainment (PTA) and cumulative fraction of response (CFR) using EUCAST data. A two-compartment model based on a data set of 19 subjects was employed. Various dosage regimens at 0.5-h and 3-h infusion rates and as continuous infusion were evaluated against the pharmacodynamic targets of 20%$fT_{>MIC}$, 40%$fT_{>MIC}$ and 100%$fT_{>MIC}$. For the target of 40%$fT_{>MIC}$, all 0.5-h infusion regimens achieved optimal exposures (CFR ≥ 90%) against *Escherichia coli* and *Staphylococcus aureus*, with nearly optimal exposure against *Klebsiella pneumoniae* (CFR ≥ 89.4%). The 3-h infusions and continuous infusion exceeded 97% CFR against all pathogens with the exception of *Pseudomonas aeruginosa* and *Acinetobacter* spp., where the maximum CFRs were 85.5% and 88.4%, respectively. For the 100%$fT_{>MIC}$ target, only continuous infusion was associated with nearly optimal exposures. Higher PTAs for the targets of 40%$fT_{>MIC}$ and 100%$fT_{>MIC}$ were achieved with 3-h infusions and continuous infusion in comparison with 0.5-h infusions; however, continuous infusion carries a risk of not reaching the MIC of less susceptible pathogens in a higher proportion of patients. In critically ill patients with HAP with risk factors for Gram-negative non-fermenting bacteria, maximum doses administered as extended infusions may be necessary.

1. Introduction

Timely initiation of antibiotic treatment, appropriate in terms of antimicrobial spectrum, is a key therapeutic intervention to reduce the mortality rate, length of hospital stay and healthcare costs in critically ill patients with infections, especially in those with sepsis [1]. This approach must be coupled with adequate dosing to maximise the effectiveness of treatment whilst preventing toxicity of the agent and minimising the development of bacterial resistance. In critically ill patients, carbapenems are ideal candidates for treatment of infections owing to their exceptionally broad antibacterial spectrum and high effectiveness [2]. However, dosing optimisation in this population remains a challenge for many clinicians, since several factors affect the achievement of optimal antibiotic exposure [3].

To optimise dosing, pharmacokinetic (PK) characteristics and pharmacodynamic (PD) targets of the agent must be considered [4]. Carbapenems display time-dependent killing. The PK/PD parameter considered to be the most predictive for therapeutic efficacy is the fraction of the dosing interval in which the unbound concentration of the antibiotic at the site of infection remains above the minimum inhibitory concentration (MIC) of the pathogen ($fT_{>MIC}$), e.g. with a target value of 40%$fT_{>MIC}$ [5].

It has been well established that the pharmacokinetics of β-lactams, as well as other hydrophilic agents, is altered in critically ill patients compared with healthy volunteers, and substantial interindividual variability is often reported [3,6]. Impaired tissue penetration has also been observed [7]. Moreover, in intensive care units (ICUs), the susceptibility patterns of causative pathogens can significantly differ from those seen in other wards [8]. Taking all these contributors into account, dosing recommendations based on studies with healthy volunteers or less seriously ill patients might not be appropriate in critically ill patients [3].

Monte Carlo simulation (MCS) is a statistical modelling technique that enables virtual clinical trials to be performed, making it highly valuable in the critical care setting where data are scarce

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Table 1
Demographics and biological and clinical characteristics of patients.[a]

Sex (no. male/female)	14/5
Age (years)	60 ± 19
Weight (kg)	76 ± 18
Height (m)	1.70 ± 0.11
BSA (m^2)	1.86 ± 0.26
CL_{cr} (mL/min)	93.2 ± 69.1
SOFA score	10 ± 4
APACHE II score	28 ± 8
ICU mortality (number of survivors/non-survivors)	17/2

BSA, body surface area (calculated by the DuBois & DuBois formula); CL_{Cr}, creatinine clearance (estimated by the Cockcroft–Gault formula); SOFA, Sequential Organ Failure Assessment; APACHE, Acute Physiology and Chronic Health Evaluation; ICU, intensive care unit.
[a] Data are the mean ± standard deviation unless otherwise stated.

Table 2
Most frequent aetiological agents (incidence ≥5%) isolated from patients with hospital-acquired pneumonia in the intensive care unit of the General University Hospital (Prague, Czech Republic) and their susceptibility rates.

Pathogen	% susceptible[a]
Klebsiella pneumoniae ($n = 185$)	100
Pseudomonas aeruginosa ($n = 106$)	48.1
Staphylococcus aureus ($n = 106$)	85.8
Escherichia coli ($n = 64$)	100
Enterobacter spp. ($n = 51$)	100
Acinetobacter spp. ($n = 30$)	100

[a] Susceptibility rates assessed according to the European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints for imipenem, i.e. 4 mg/L for *P. aeruginosa* and 2 mg/L for other detected species. No strains with intermediate susceptibility were isolated.

[4]. MCS can evaluate the likelihood of achieving the predefined therapeutic targets with various dosage regimens in a specific patient population, provided the PK parameter estimates and their distribution in the population have been established [9].

The objectives of this study were to evaluate the population pharmacokinetics of imipenem in critically ill patients with hospital-acquired pneumonia (HAP) and to assess PD characteristics, expressed as the probability of target attainment (PTA) and cumulative fraction of response (CFR), using MCS methods.

2. Materials and methods

2.1. Patients

PK data from a previously published prospective randomised PK study of critically ill patients with HAP who had been treated with imipenem/cilastatin were included [10]. The population involved 19 non-obese adult subjects without hepatic dysfunction or renal failure. Baseline demographic, biological and clinical characteristics of the source patient population are summarised in Table 1. The study protocol was approved by the local ethics committee. For more details on the study population, sampling and analytical methods, refer to Lipš et al [10].

2.2. Pharmacokinetic analysis

For the PK analysis, PMetrics, the non-parametric modelling package for R (Laboratory of Applied Pharmacokinetics and Bioinformatics, University of Southern California, Los Angeles, CA) [11], employing the non-parametric adaptive grid (NPAG) algorithm [12] was used.

Based on model performance and previously published data related to imipenem pharmacokinetics and modelling [13], a two-compartment model with zero-order input (intermittent infusion of 0.5-h or 3-h duration, respectively, and continuous infusion, in each case preceded by a 1 g loading dose administered by a 0.5-h infusion) and first-order elimination was employed.

The model was built in an iterative fashion. Different demographic, biological and clinical covariates were tested for their ability to improve the model prediction of imipenem kinetics as measured by the log likelihood, Akaike information criterion (AIC), Bayesian information criterion (BIC) and observation–prediction plots. If the covariate inclusion improved the log likelihood ($P < 0.05$) and/or the goodness-of-fit plots, they were included in the model. An additive error model was used to weigh the concentrations by $[(S.D. + \lambda)^2]^{-1}$, where S.D. is the standard deviation and λ is representative of additional noise, such as errors in the sample or dose timing or model misspecification.

In addition to the AIC and BIC, the final model was selected based on minimisation of the weighted mean error as a measure of bias and of the bias-adjusted weighted mean squared error as a measure of precision. Normalised prediction distribution error (npde) plots were used to assess the predictions generated by each model [14]. The npde was based on 1000 simulated profiles per subject, using their own weight, imipenem dosing history, sampling schedule and the final population model parameter value means and covariances as the prior from which each simulated set of parameter values was generated.

For the npde simulations and PD analysis, a Monte Carlo approach takes a multimodal multivariate distribution from which it samples. This approach is better in preserving the heterogeneity of the ICU patient population than the population-wide parametric approach [15].

2.3. Pharmacodynamic analysis

Using the Bayesian posterior values of the model, 10,000 individual free serum concentration–time profiles following the fourth dose were generated for each of the following dosing regimens: 500 mg every 6 h (q6h); 500 mg every 4 h; 750 mg every 8 h (q8h); 750 mg q6h; 1 g q8h; and 1 g q6h (each as a 0.5-h and 3-h infusion); and a continuous infusion of 3 g/day. These doses were selected to represent the most common dosing range according to the drug label. Upon request of the reviewers, higher daily doses (i.e. 6 g/day as well as continuous infusion of 4 g/day and 5 g/day, which may be used off-label by some centres) were additionally simulated. As a conservative approach, the protein binding of imipenem was assumed to be 20% in order not to overestimate the free levels [2]. Subsequently, the PTA characterised as the fraction of subjects attaining the predefined PD target was calculated for each regimen using the PD targets of $40\%fT_{>MIC}$ and $100\%fT_{>MIC}$. Dosing regimens achieving a PTA of ≥90% were considered to be optimal. A target of $20\%fT_{>MIC}$ was also evaluated to assess the risk of failing to reach even this minimum bacteriostatic threshold.

The imipenem MIC distributions of the most frequent aetiological agents causing HAP [16] were obtained from the European Committee on Antimicrobial Susceptibility Testing (EUCAST) [17] and, for comparison, local susceptibility data were also considered. Over a 6-year period (2010–2015), 555 non-duplicate consecutive isolates were obtained from endotracheal aspirate or bronchoalveolar lavage fluid samples in individual critically ill patients with HAP admitted to the general ICU of the General University Hospital (Prague, Czech Republic). The most commonly detected bacterial species included *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Escherichia coli*, *Enterobacter* spp. and *Acinetobacter* spp. (for frequencies and susceptibility rates, see Table 2). MIC testing was performed by Etest (AB BIODISK, Solna, Sweden) according to the manufacturer's recommendations. For *S. aureus*, the local MIC dis-